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Normal tissue complication probability of fibrosis in radiotherapy of breast cancer: Accelerated partial breast irradiation vs conventional external-beam radiotherapy

KS Jothy Basu, Amit Bahl, V Subramani, DN Sharma, GK Rath, PK Julka

Department of Radiation Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi-110 029, India

For correspondence:
Dr. Amit Bahl, Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi-110 029, India. E-mail: dramitbahl@yahoo.com

ABSTRACT

Aims: Radiotherapy forms an integral part of breast-conserving treatment in early-stage breast cancer. Subcutaneous fibrosis of the treated breast is an important late effect in whole-breast irradiation. The aim of this study was to compare the normal tissue complication probability (NTCP) for radiation-induced fibrosis in treated breast using accelerated partial-breast irradiation (APBI) vs conventional treatment.

Materials and Methods: Ten postoperative early-stage breast cancer patients (T1N0M0) were included in this dosimetric analysis. APBI treatment was planned using conformal radiotherapy technique and conventional treatment plans included two tangential portals. All the APBI treatment plans were made with five non-coplanar beams with 6 MV photons. The prescription dose was 38 Gy in 10 fractions for the APBI treatments and 50 Gy in 25 fractions, followed by a boost dose of 16 Gy in 8 fractions, for the conventional treatments. We used Lyman's relative-seriality model and the breast fibrosis NTCP model fitting parameters for the study.

Results: The equivalent uniform dose (EUD) was 30.09 Gy and 50.79 Gy in APBI and conventional treatment, respectively. The mean NTCP values for ipsilateral breast fibrosis in APBI and conventional treatment were 0.51 and 25.66%, respectively. Using the paired t-test, a statistically significant difference was seen in the breast fibrosis NTCP values for APBI vs conventional treatment ($P<0.001$).

Conclusions: APBI reduces the ipsilateral breast fibrosis compared to conventional whole-breast treatment in early-stage breast cancer.

KEY WORDS: Accelerated partial breast irradiation, breast, normal tissue complication probability

INTRODUCTION

Breast -conserving treatment involving whole breast radiotherapy is a well-accepted treatment modality in women presenting with early-stage breast cancer.[1,2] However, concerns over long-term cosmetic, cardiac, and pulmonary toxicity are increasingly being debated. As treatment techniques become more refined, the focus on cosmetic outcome is increasing. Fibrosis is one of the important long-term sequelae seen in irradiated breasts using conventional tangential fields and has an significant impact on the cosmesis and quality of life of the patients. A grade III–IV fibrosis of 10–16% has been seen in patients on longer follow-up.[3] Using limited radiotherapy fields is one way of decreasing this treatment-related morbidity. Conformal radiotherapy techniques like intensity-modulated radiotherapy (IMRT) has been shown to reduce chronic breast edema after treatment.[4] However, an increase in late normal tissue toxicity has also been reported using IMRT in breast cancer treatment due to a larger volume of tissue receiving sub-prescription doses.[5] Accelerated partial breast irradiation (APBI) appears to be another promising modality for reduction of chronic treatment-related effects.[6] APBI treatment can be delivered either by brachytherapy using mammosite or interstitial techniques or with external-beam radiotherapy using conformal portals.

Though dosimetric comparison of different techniques used to deliver APBI have been reported, none of these studies have used normal tissue complication probability (NTCP) modeling to quantify post-treatment fibrosis.[7] NTCP models can help us predict the expected long-term fibrosis in treated patients and help compare different treatment techniques. In this dosimetric study we have used the relative-seriality model to predict NTCP for fibrosis in treated breasts using APBI delivered with conformal 3D external-

beam technique and whole-breast conventional tangential treatments followed by electron boost.

MATERIALS AND METHODS

Ten postoperative early-stage breast cancer cases (T1N0M0) were included in this dosimetric study. CT images of all the cases were acquired with a slice thickness of 2.5 mm with the patient immobilized in the treatment position. The lumpectomy cavity was identified with the help of surgical clips. Eclipse™ (Varian Associates, Palo Alto, CA) treatment-planning system was used for contouring and planning. A uniform margin of 2 cm was given to the gross tumor volume (GTV) to clinical target volume (CTV) and a uniform margin of 1 cm was given to the CTV to planning target volume (PTV). The target volume outside or close to the skin was removed with a skin-to-target margin of 5 mm. To calculate the NTCP of the ipsilateral breast fibrosis we subtracted the target volume from the normal breast tissue using Boolean functions available in the treatment planning system and named it normal ipsilateral breast tissue (NIBT). A detailed description of the treatment planning and radiobiological model used in the study is given below.

Treatment planning

All the conventional initial-phase and APBI treatment plans were planned using 6 MV photons. The conventional treatment comprised an initial-phase treatment followed by a boost treatment with electron beam to the primary tumor. The initial-phase treatment was planned using conventional photon tangential fields with SSD (source-to-skin distance) technique. The field parameters such as field weight, wedge angle, and collimator angle were chosen so as to achieve maximum coverage and dose uniformity in the region of interest. The boost treatment was planned with electrons in the energy range of 9–16 MeV, depending upon the target coverage and dose uniformity achievable for the selected patient. The prescription doses were 50 Gy in 25 fractions for the initial-phase and 16 Gy in 8 fractions for the boost-phase. The field arrangements are shown in Figure 1a and b.

APBI treatment was planned with a combination of five coplanar and non-coplanar beams with 6 MV photons with isocentric technique. Wedges were used wherever necessary to increase the dose uniformity. The prescription isodose level was chosen such that at least 95% of the target volume would receive the prescription dose. The prescription dose was 38 Gy in 10 fractions for the APBI treatment. The field arrangements are shown in Figure 2a and b.

NTCP model

The NTCP model used in this study is entirely based on the

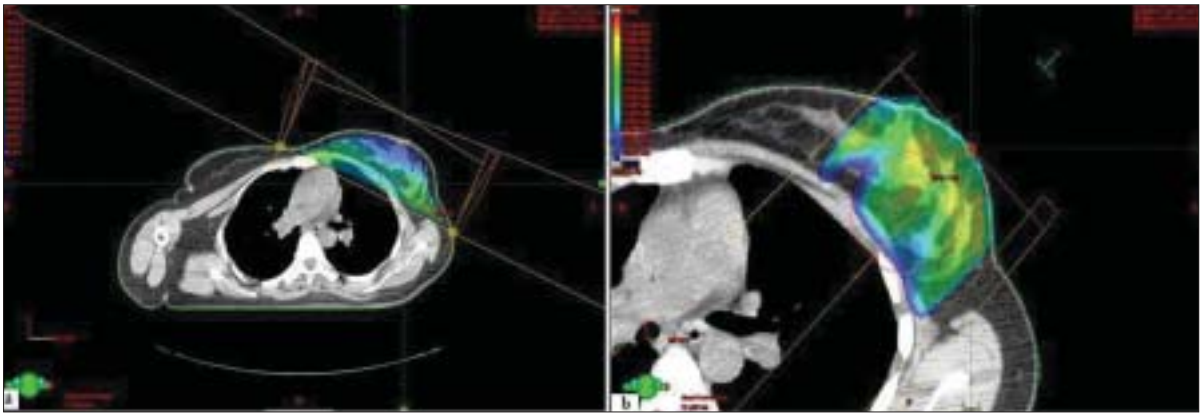

Figure 1: (a) Beam arrangements for conventional tangential and (b) electron boost treatment

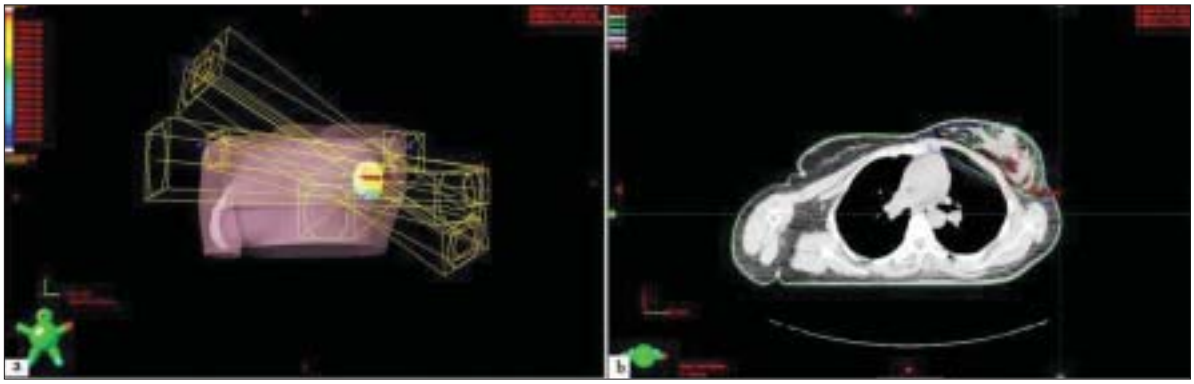

Figure 2: (a) Beam arrangement for APBI and (b) resulting dose distribution

model fitting parameters calculated by Alexander *et al*. and the relative-seriality model proposed by Källman *et al*.[8] The relative-seriality model, which is based on the Poisson model of cell survival, gives the probability P(D, v) of cell death when a fractional volume v is given a dose D [Equation 1]:

$$P(D, v) = 2^{-\exp[e\gamma(1-D/D_{50})+\ln(v)]} \quad (1)$$

Where γ is the slope of the dose–response curve at 50% response and D_{50} is the dose to cause a given effect in 50% of the population. In this we have replaced D by equivalent uniform dose (EUD) and D_{50} by EUD_{50}. EUD_{50} is 62.4 Gy in conventional fractionation as calculated by Alexander *et al*. Using this probability model the NTCP is calculated as follows:

$$NTCP = \left(1 - P(D,v)^s\right)^{v^{\frac{1}{s}}} \quad (2)$$

Where s describes the hybrid serial/parallel architecture of the organ, a large value of s indicates a serial structure, and a small value indicates a parallel structure. An s value of 0.12 is used in this study as calculated by Alexander *et al*.

For the purpose of calculating EUD the dose matrices of the initial and boost phases were summed for the conventional treatment. The differential dose–volume histograms (DVH) of the NIBT were used to calculate the EUD with 'a' value of 0.78 as calculated by Alexander *et al*., using Equation 3 proposed by Niemeirko[9]:

$$EUD = \left(\sum \frac{v_i}{V_{Total}} (D_i)^a\right)^{\frac{1}{a}} \quad (3)$$

Where v_i is the fractional volume irradiated to dose D_i, V_{Total} is the total volume of the structure, and 'a' is the tissue-specific model fitting parameter.

For the APBI plans the individual voxel doses were converted to conventional fractionation doses using the classical biologically equivalent dose (BED) equation [Equation 4]; the voxel equivalent doses (VED) were then used to calculate the EUD for equivalent fractionation.[10]

$$BED = D\left(1 + \frac{d}{\left(\frac{\alpha}{\beta}\right)}\right) \quad (4)$$

Where D is the total dose delivered, d is the dose per fraction, and α/β is a tissue-dependant parameter. In this study, we used an α/β value of 3, as normal breast parenchyma behaves as late-reacting tissue.

RESULTS

In the APBI patients the mean EUD was 30.09 Gy and it was 50.79 Gy in conventional treatment. The mean NTCP values for ipsilateral breast fibrosis APBI and conventional treatment were 0.51 and 25.66%, respectively. Using paired t-test, a statistically significant difference was seen in the breast fibrosis NTCP values for APBI vs conventional treatment ($P < 0.001$) [Figure 3]. The doses to other critical structures like heart and lungs are minimal and can be considered negligible. The bar charts for EUD and NTCP are shown in Figures 4 and 5 for APBI and conventional treatments. The equivalent cumulative DVH is shown in Figure 6 for normal ipsilateral breast tissue for APBI and conventional treatments.

DISCUSSION

Radiation-induced fibrosis is influenced by a number of factors like age, nutritional status, coexisting morbidity, surgery, and biological differences between patients. Radiotherapy-related factors can also play a major role in determining the extent of

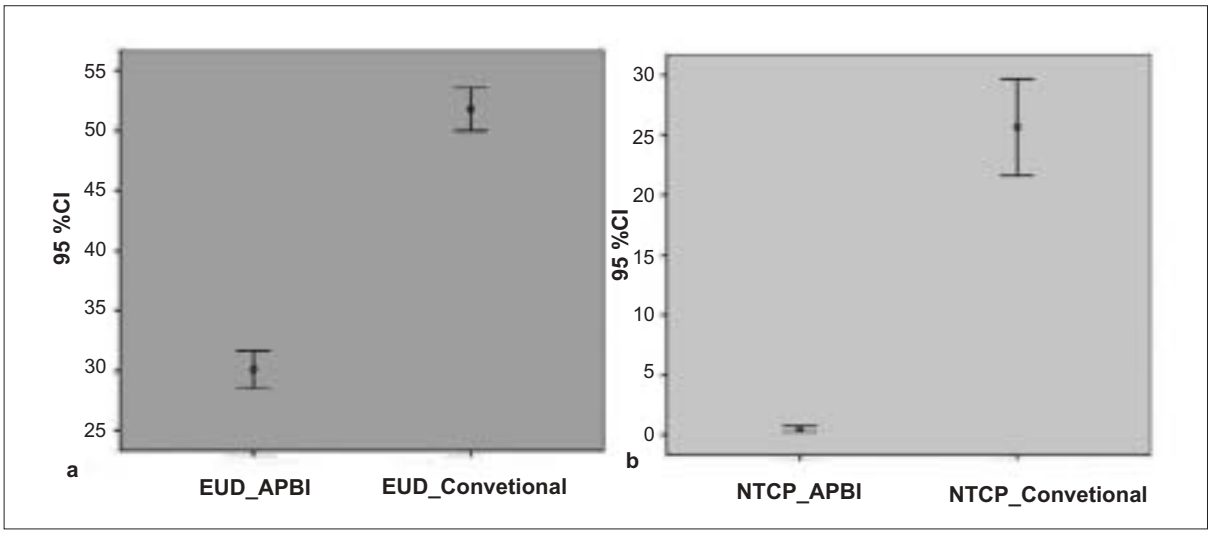

Figure 3: Errors bars for (a) EUD and (b) NTCP

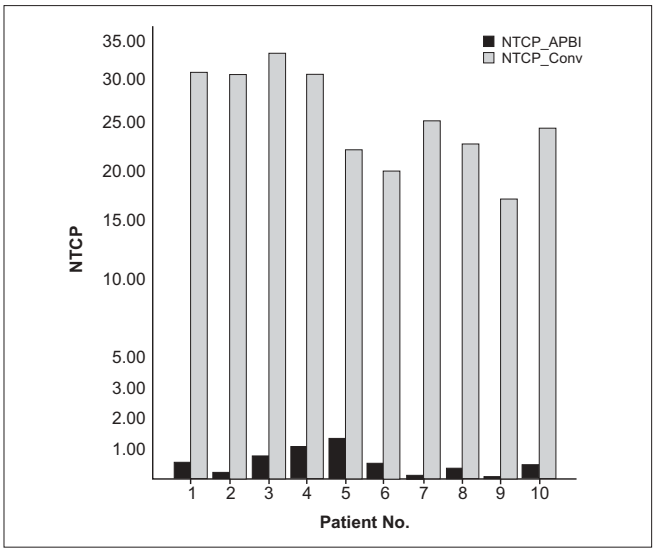

Figure 4: NTCP for treatment related fibrosis in early-stage breast cancer in APBI vs conventional treatment

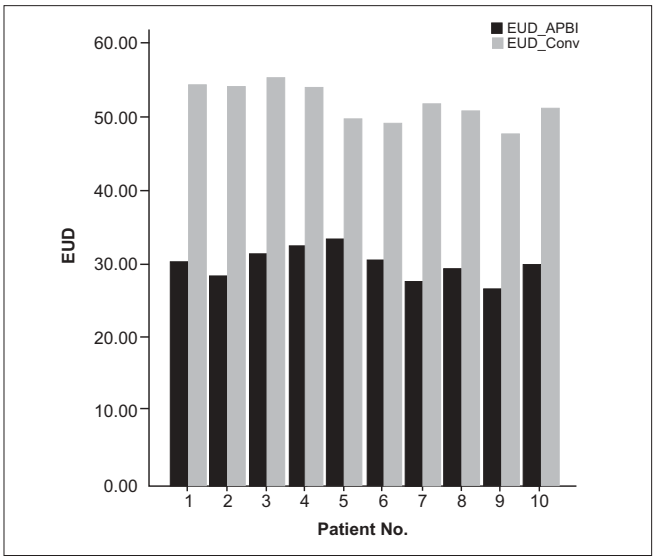

Figure 5: EUD for conventional and APBI treatments

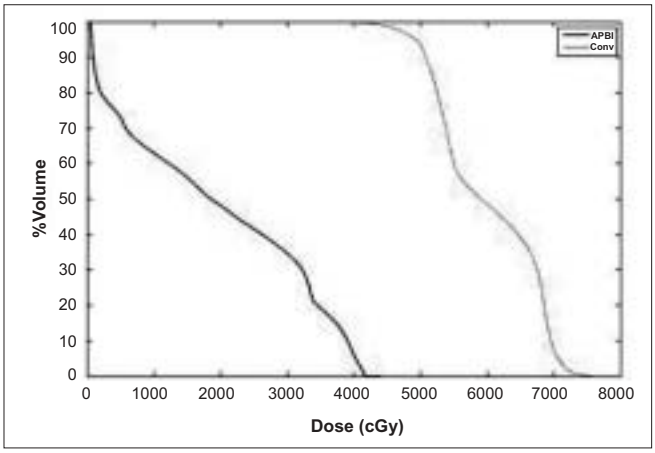

Figure 6: DVH for APBI and conventional treatment for NIBT

fibrosis. Cosmetic outcome is important in breast-conserving treatment, and doses above 50 Gy used in whole-breast radiotherapy are known to be associated with a poor cosmetic outcome.[11] Our study has shown the superiority of APBI delivered by 3D conformal radiotherapy over conventional treatment in reducing radiation-induced fibrosis in ipsilateral breast. APBI using 3D conformal radiotherapy has been shown to be almost equivalent to multicatheter brachytherapy and mammosite brachytherapy in terms of EUD and tumor control probability.[12] Alexander *et al*. have analyzed NTCP for fibrosis in breast, comparing IMRT with conventional treatment methods. Their results showed increased NTCP with IMRT treatments due to increased dose to areas receiving sub-prescription doses.

APBI is expected to reduce breast fibrosis more than conventional whole-breast radiotherapy; however, there are very few studies that have attempted to calculate the NTCP for breast fibrosis, probably due to lack of radiobiological model fitting parameters. We have attempted to quantify the fibrosis complication probability in APBI and conventional treatment. Such radiobiological models will be of great help for designing individualized treatments for patients and also to assess the prescription dose. Even though these radiobiological models are highly dependant on the model fitting parameters, it can be used to compare plans where the relative difference is less likely to be affected by input parameters.

However, an APBI treatment protocol needs to be carefully implemented. Delineation of the lumpectomy cavity can be a source of error. APBI treatments should not be attempted unless the lumpectomy cavity can be clearly identified with the help of surgical clips placed at the time of surgery. The issue of organ motion also needs to be addressed. Using image-guided radiotherapy or an active breathing coordinator may be a way out. In the absence of such sophisticated equipment, a slightly larger PTV can be taken to compensate for respiratory motion. Many of these issues call for a larger randomized study to be undertaken.

CONCLUSIONS

APBI planned by conformal techniques scores over conventional techniques in reducing fibrosis in treated breast. Our study also underlines the importance of using biological indices in routine plan evaluation comparing different treatment techniques and competing plans.

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